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(21) International Application Number: PCT/DK99/00434 (22) International Filing Date: 13 August 1999 (13.08.99) (30) Priority Data: PA 1998 01033 14 August 1998 (14.08.98) DK (71) Applicant (for all designated States except US): COLOPLAST A/S [DK/DK]; Høltedam 1, DK-3050 Humlebaek (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): PEDERSEN, Lars, Hastrup [DK/DK]; Kvisten 34, DK-9260 Gistrup (DK). SAMUELSEN, Peter, Boman [DK/DK]; Bukkebaallevej 18, DK-2960 Rungsted Kyst (DK). LARSEN, Kim, Lambertsen [DK/DK]; Lemvigvej 90 A, st., DK-9220 Aalborg Øst (DK). (74) Common Representative: COLOPLAST A/S; Nilausen, Kim, Patent Dept., Høltedam 1, DK-3050 Humlebaek (DK).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: STABILISED COMPOSITIONS HAVING ANTIBACTERIAL ACTIVITY (57) Abstract A stabilised composition having antibacterial, antiviral and/or antifungal activity characterised in that it comprises a silver compound and that the compound is in the form of a complex with a primary, secondary or tertiary amine which complex is associated to one or more hydrophilic polymers is stable during sterilisation and retaining the activity without giving rise to darkening or discoloration of the dressing during storage.		

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TITLE

Stabilised compositions having antibacterial activity

FIELD OF THE INVENTION

The present invention relates to stabilised compositions having antibacterial, anti-
5 viral and/or antifungal activity, to a method of producing such compositions, medical devices having a coating comprising such compositions, and the use of the stabilised compositions for producing a wound dressing, an ostomy appliance, an incontinence device, other medical devices or hydrophilic coatings.

BACKGROUND OF THE INVENTION

- 10 The antiseptic activity of silver compounds is a well known property which has been utilised for many years. The bacteriostatic and fungistatic effect is caused by the silver ion and a simple compound which has been used clinically is for instance silver nitrate. Silver nitrate in concentrations of 0,5 - 1% in water shows disinfectant properties and is used for preventing infections in burns or for
15 prophylaxis of neonatal conjunctivitis. For another silver compound, silver sulfadiazine, the antibacterial effect of the sulfadiazine molecule is further enhanced by the complexing with the disinfecting silver ion. In contrast to the silver-nitrate, the solubility of the silver sulfadiazine complex is low and hence, both of the two active parts are only present in solution in low concentrations but may be present
20 over a longer period of time before being washed out at site to be treated. The silver sulfadiazine is intensively used in the treatment of wounds, in particular burns, under the trademarks Silvadene® and Flamazine®. Silver-protein-combinations are yet other antiseptic formulations which have been used in low concentrations as eye drops.
- 25 Bacteriostatics based on the silver ion are further used in various medical devices. One example of such application is the use in the wound dressing sold by Johnson & Johnson under the trademark Actisorb® which is an activated charcoal cloth dressing. Another example is the wound dressing sold under the

trademark EZ-Derm by Genetic Laboratories which dressing is a modified pigskin impregnated with a soluble silver compound intended for treatment of burns.

A number of patents discloses compositions or devices showing antiseptic properties based on contents of silver compounds. EP 272 149 B1 discloses a
5 medical dressing of the 'hydrocolloid' type containing and releasing active components. Silver chloride is a specific antiseptically acting compound mentioned in this patent.

A specific advantage in using the silver ion as bacteriostatic agent is the general lack of formation of bacterial tolerance to the compound. This is in contrast to
10 many types of antibiotics. However a major drawback when using ionic silver for bacteriostatic purposes is the reduction of the ion to free silver which results in dark stainings. Such staining has been reported to give potentially permanent pigmentation of the skin, the so-called argyria. It is commonly recognised that silver containing compounds will discolour by influence of light and or heat, and it
15 will often be found that sterilisation by radiation may lead to a unsatisfactory change of the colour of a composition in which it is comprised, irrespective of the use in a solution, cream or gel or a medical device. Furthermore, such antibacterial compositions are often intended used in connection with medical or cosmetic products under circumstances where a discoloration is very unfortunate and
20 potentially precluding for the use.

Recently, principles of antimicrobial metal-based compositions being photo stable, have been disclosed in US Patent No. 5,326,567 to Capelli and in US Patent No. 5,429,819 to Oka. In US Patent No. 5,326,567 a 'host-guest' relationship between silver ions and acyclic polyethers is accomplished through the use
25 of excess of halide ions. In US Patent 5,429,819 is disclosed a photo-stable composition comprising a complex of the silver ion with a thiosulphate salt carried on a porous particulate carrier. In US Patent No. 3,911,115 (DE patent No. 22 60 536) a cycloheptaamylose (β -cyclodextrin) alkanol amine compound is claimed to posses stabilising effect on silver. However, in praxis the cycloheptaamylose
30 alkanol amine complex is not effective in preventing discolouring and furthermore,

for medical purposes it is disadvantageous to introduce an alkanol giving rise to formation of a toxic carrier complex for the silver as the alkanolamines generally are known as irritants and moderate toxic compounds having numerous potential side effects (Patty's Industrial Hygiene and Toxicology, Vol II, Part B, 4th ed. 5 1994).

It is commonly recognised that compounds containing silver will discolourise in presence of light and or heat, as well as it often will be found that radiation sterilisation process will lead to a dissatisfactory change of colour of the composition in which it is comprised whether it is in a cream or a gel or a medical device. Moreover, such antibacterial compositions are often intended for use for medical or 10 cosmetic purposes under which circumstances a discoloration is very unfortunate and potentially prevents the use of silver ions for said use.

None of the above references describe examples of hydrophilic polymer formulations or devices comprising such formulations containing silver compounds for 15 use as antiseptic being stable against discoloration due to reduction of the silver ion or being stable against potential conversion of the silver ion into the dark stained compounds of silver such as metallic silver or the silver sulphide.

It is an object of the present invention to provide complex structure rendering silver ions stable against loss of the antiseptic activity and against darkening due 20 to reduction of the silver ions or the formation of darkly stained sparingly or insoluble silver compounds.

Further it is an object of the invention to provide principles and methods of introducing the silver compositions stabilised against the effect of light into catheters guide-wires or similar medical devices or instruments.

25

It has now surprisingly been found that silver ions may effectively be stabilised against exposure to light by formation of simple complexes with primary, secondary or tertiary amines which complexes are associated to hydrophilic polymers.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to stabilised compositions having antibacterial, antiviral and/or antifungal activity.

Furthermore, the invention relates to a method of producing compositions having
5 antibacterial, antiviral and/or antifungal activity.

Still further, the invention relates to medical devices having a coating comprising compositions having antibacterial, antiviral and/or antifungal activity.

The invention also relates to the use of the stabilised compositions having antibacterial, antiviral and/or antifungal activity for producing a wound dressing or
10 an ostomy appliance, an incontinence device, other medical devices or hydrophilic coatings.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a stabilised composition having antibacterial, antiviral and/or antifungal activity which composition is characterised in that it
15 comprises a silver compound in the form of a complex with a primary, secondary or tertiary amine which complex is associated to one or more hydrophilic polymers.

The amine being used in the compositions of the invention are suitably a primary, secondary or tertiary lower alkyl amine or amino alcohol having a free lone pair of
20 electrons.

A lower alkyl amine is preferably selected from mono, di or tri methyl, ethyl, propyl or butyl amines or mixtures thereof.

A lower alkyl amino alcohol is preferably selected from mono, di or tri methyl ethyl or propyl aminoalcohols or mixtures thereof.

The compositions of the present invention will show alkaline properties in aqueous solutions and the pH may be adjusted to a value from 6.5 to 8.5 or/or neutralised using an appropriate acid such as a mineral acid such as hydrochloric acid.

- 5 Without restricting the invention to any specific theory, it is believed that the stabilisation of the silver compound is to be ascribed to a formation of a complex between the silver ion and the amines offering a free lone pair of electrons for complexation. Surprisingly this type of silver complexes have been shown to be stable not only in dry conditions but also in aqueous solutions containing ionic
- 10 polymers such as various types of derivatized polysaccharides which are often used in hydrogels or other types of wound dressings. Furthermore, medical devices such as catheters, stents or guide wires often contain the antibacterial substance in a hydrophilic coating which may otherwise destabilise the silver under processing or storage if it is not in a stabilised form.
- 15 Thus, it is assumed that silver salts may be stabilised in solution by amines in which the nitrogen atom has an active free lone pair of electrons. For the purpose of the present invention the term "stabilisation" is intended to cover an improvement of the stability of the silver ion against the influence light and heat which normally leads to formation of dark stained free silver.
- 20 It is known that solutions of silver salts may fairly easily be stabilised against heat and light when stabilised with dextrans and thiosulfates. These types of complexes has, however, shown not to be stable in presence of hydrophilic polymers especially the strongly polar or ionic polymers. The stabilisation of silver with the amines according to the present invention also provides stability in the
- 25 presence of such polymers. As ionic and polar polymers are used increasingly in medical devices and as silver compounds are effective antibacterial agents combinations of these are very desirable. The present invention offers the option of using such combinations without risking discoloration as well as methods of producing compositions comprising and medical devices comprising the same.

None of the above references teach the complexation between silver compounds and primary, secondary or tertiary and moreover do not teach the stabilisation of complexes associated to hydrophilic polymers against discoloration.

The hydrophilic polymers used in the compositions according to the invention are
5 suitably selected from synthetic hydrophilic polymers and derivatives of animal or vegetable hydrophilic polymers. In a preferred embodiment of the invention the hydrophilic polymer is selected from the polysaccharides. Polysaccharides to be used according to the invention are preferably cellulose derivatives. Preferred cellulose derivatives are sodium carboxymethylcellulose and
10 hydroxyethylcellulose.

In another embodiment of the invention the hydrophilic polymer is selected from the alginates. An alginate is preferably the sodium alginate.

In yet another embodiment of the invention the hydrophilic polymer is selected from collagens. Preferably porcine collagen is used.

~~15~~ In yet further embodiments of the invention the hydrophilic polymer is selected from glucosaminoglycans and proteoglycans

In still another, preferred embodiment the composition according to the invention is a hydrophilic polymer which forms a gel or xerogel.

The polymers to be used in the compositions of the present invention may be in
20 the form of a polymer forming a network of crosslinked or non crosslinked hydrophilic polymer.

Preferably the hydrophilic polymer is a polysaccharide and preferably from the group of the cellulosic derivatives having various substituents. Such polymers are readily available from the nature or from synthetic modification. Other preferred
25 polymers are polylactic acid, polyhydroxybutyrates or similar polyesters, polyvinyl

alcohol, polyvinylporrolidone, polyacrylates, hydrophilic polyurethanes, polymaleic acid and polymers of natural origin like glucosaminoglycans, collagen and fibrin or the like as well as copolymers or derivatives thereof.

Further, such polymers may be crosslinked into three dimensional networks.

- 5 Silver salts to be used according to the invention may be readily soluble salts like the nitrate, lactate, or acetate or more heavily soluble salts like the halogenides such as the chloride or bromide. The silver salt is preferably silver nitrate, silver acetate or silver lactate. Thus, the choice of silver compound for the purpose of the present invention is not critical.
- 10 The concentration of silver in the composition according to the invention is preferably from 0.1 to 30 % by weight of the dry matter, more preferred from 0.5 to 5 % by weight of the dry matter.

The compositions of the invention may be e.g. used in wound dressings. In particular the material is suitable for incorporation in traditional gauzes and
15 ~~compresses, hydrocolloid dressings or xerogel dressings.~~ In such dressings the silver composition according to the invention is readily incorporated by dissolution in water and impregnation into dressings like gauze, or they may be introduced as a component of said dressing, e.g. a component of an adhesive composition, by a manner known per se. A method for incorporation in hydrocolloid dressings
20 is disclosed in GB Patent 591,440, Samuelsen et al. A method for incorporation of the composition in alginate fibre dressings or similar dressings is by simply adding the composition to the solution comprising the alginate before this is further processed into a fibrous material. Introduction may also take place in the form of a powder which is easily obtained for instance by grinding a lyophilised or
25 spray-dried material. In wound dressings the compound may be introduced into the adhesive for fixing the dressing to the wound site or into another part of the dressing, for instance a foam pad.

The compositions of the invention and formulations thereof may be used for antibacterial, antiviral or antifungal use in the area of human or veterinary medicine. Such formulations may be in the form of a cream or gel intended for dermatological use on skin, in wounds or other body cavities. Formulations may
5 also be in form of powders for similar purposes or for skin folds or athletes foot or the like in the veterinary area.

The antibacterial property may not be the intended and most important property of such formulations but an concomitant property.

Many other types of products are suitable for incorporation of the silver composi-
10 tions of the invention for instance foam or other vaginal inserts for use in the continence care, condoms, male external urine catheters, skin adhesives etc. Furthermore, the compositions may be used in products not necessarily being in direct contact with the body such as powders for removal of odour in incontinence pads or for incorporation into ostomy pouches.

15 The silver compositions of the invention may also be used in implants and ~~sutures or materials that for a period will be left in body cavities.~~ This will be advantageous in connection with surgery where the risk of infection is always latent. Systemic prophylactic treatment with antibiotics in combination with a proper antiseptic treatment of the skin are in most cases common practice. Often
20 medical articles that are implanted or for other reasons left in a surgical opening are carrying antiseptics or even antibiotics. The present invention offers an advantageous alternative to known compositions comprising silver as the composition of the invention has broad antiseptic properties and secures stability during storing and in use. Moreover it is very suitable for controlled release for instance
25 when incorporated in polylactic acid for sutures or implants or when incorporated in implants based on hydroxyl apatite. Furthermore, the silver compositions of the invention are suitable for incorporation into haemostats based on e.g. alginate fibre or foam dressings as well as materials based on collagen or gelatine. Still

further, the compositions may be introduced into gel-like materials intended to be protecting covers for e.g. anastomoses formed in bowel or vascular surgery.

The invention also relates to a medical device comprising an impregnation or coating comprising a silver compound in the form of a complex with a primary,
5 secondary or tertiary amine which complex is associated to one or more hydrophilic polymers.

Furthermore, the invention relates to a method of producing compositions having antibacterial, antiviral and/or antifungal activity in which a silver salt is dissolved in water, an amine is added and the resulting solution is left for a period of from 2 to
10 100 hours, optionally after adjusting the pH using an acid, the resulting mixture is added to a hydrophilic polymer and optionally dried and micronised.

Still further, the invention relates to the use of stabilised compositions comprising a silver compound in the form of a complex with a primary, secondary or tertiary amine which complex is associated to one or more hydrophilic polymers, said
15 composition having antibacterial, antiviral and/or antifungal activity for producing ~~a wound dressing, an ostomy appliance, an incontinence device, other medical~~ devices or hydrophilic coatings.

The invention is explained more in detail in the working examples below disclosing embodiments and properties of compositions of the invention. It is evident that
20 many variations may be made without diverging from the invention the scope of which is set forth in the appended claims.

MATERIALS AND METHODS

EXAMPLE A

Preparation of a stock solution of silver nitrate

25 A stock solution of silver nitrate was prepared by dissolving silver nitrate in distilled water to a concentration of 1.5 molar.

EXPERIMENTAL PART

REFERENCE EXAMPLE 1

Preparation of a silver compound as disclosed in DE patent 22 60 536 and a composition comprising the same.

- 5 51 grams of beta-cyclodextrin was dissolved in 100 ml ethanolamine under stirring at 80 °C. The solution was cooled to 35 °C in an ice bath. 10 grams of silver nitrate was added under stirring until a clear solution was obtained. Further 205 ml of warm ethanolamine having a temperature of 35°C was slowly added whereafter the solution is filtered through a Whatman No. 1 filter.
- 10 The resulting solution was cooled to 5 °C for precipitation over 24 hours. The precipitate was filtered from the residual ethanolamine and washed with cold acetone (7 times 80 ml) until no more silver can be detected in the washing liquid.

A gel of sodium-carboxymethylcellulose containing the complex as above was produced from 100 ml distilled water, 4 g sodium-CMC and 0.67 g of the purified
15—complex—obtained—above—in—an—analogous—manner—as—described—in—Example 1.

The resulting composition contained 1% silver, based on dry weight.

REFERENCE EXAMPLE 2

Preparation of a CMC gel comprising silver nitrate.

- A gel composed of 4 % sodium carboxyl cellulose was produced by adding the
20 polymer in an amount of 4 g/100 ml to a silver nitrate solution of a concentration of 0.068% by simple dissolving at ambient temperature using a stirrer over 8 hrs.

EXAMPLE 1

Preparation of a stabilised silver compound according to the invention.

To 0.5 ml of the 1.5 molar solution was added 3.7 ml of 1.8 molar tri-hydroxymethyl-aminomethane titrated to pH 6.9 using 1.0 N hydrochloric acid.

- 5 The silver-amino complex was equilibrated for 72 hours at ambient temperature in the dark.

Finally, 200 ml distilled water and 8 g sodium-carboxymethyl-cellulose were added to the complex.

The resulting composition contained 0,036 molar silver complex in a 3.9 %

- 10 Carboxymethylcellulose gel.

EXAMPLE 2

Preparation and lyophilization of a stabilised silver compound according to the invention.

A composition prepared in the same manner as disclosed in Example 1 was

- 15 lyophilised over night and micronized to a powder with average particle size of 20 - 50 micrometers. The resulting powder contains 0.95% silver.

EXAMPLE 3

Preparation of a stabilised silver compound according to the invention

- To 0.5 ml of 1.5 molar solution of silver nitrate was added 2.9 ml of 1,8 molar
20 trimethyl-aminomethane titrated to pH 7.5 with 1.0 N hydrochloric acid.

The composition was allowed to stand for 72 hours in the dark at ambient temperature. To the resulting solution were added 200 ml distilled water and 4 grams of sodium-carboxymethylcellulose were added to the silver complex .

- The resulting composition contained 0.036 molar silver complex in 2.0% carboxy-
25 methylcellulose gel.

EXAMPLE 4

Preparation of a stabilised silver compound according to the invention.

In the same manner as disclosed in Example 1 a stabilised silver compound was produced using sodium alginate instead of carboxymethylcellulose.

5 EXAMPLE 5

Preparation of a stabilised silver compound according to the invention comprising hydroxyethyl cellulose.

Silver nitrate was dissolved in distilled water in a concentration of 1.0 molar. To 1 ml of the solution was added 2 ml of a 1.5 molar solution of ethylamine. The
10 mixture was titrated to pH 8.0 with 1.0 molar hydrochloric acid and allowed to stand for 48 hours at ambient temperature in the dark.

To the composition was added 100 ml of a solution of 2.0 % hydroxyethyl cellulose in distilled water.

The resulting composition contains 0,09 molar silver complex.

15 EXAMPLE 6

Preparation of a stabilised silver compound according to the invention.

In the same manner as disclosed in Example 1 a stabilised silver compound was produced using porcine collagen instead of carboxymethylcellulose.

EXAMPLE 7

20 Comparison of Stability Against Discoloration of Compositions According to the Invention and of Known Compositions

Stability against discoloration was determined in two ways as follows:

A: Stability to heat was determined by heating of the composition at 120 °C for 75 minutes for dry and gel compositions.

B: Stability to light was determined by exposure of sample to a light source fluorescent tube (Osram L 58W/31-800) for 24 hours. Discoloration was determined spectrophotocally of a diluted gel sample in water (1:10) at a wave length of 425 nm using a Perkin Elmer UV/VIS spectrometer Lambda 2.

- 5 The results are summarised in the below Table 1 stating stability of compositions according to the invention prepared according to Examples 1 - 5 as compared to non stabilised compositions of Reference Examples 1 - 2.

Table 1. Stability against discoloration by UV light and heat

Example	UV - discoloration index *	Heat - discoloration index**
1	0.06	Clear
3	0.07	Clear
4	0.1	Clear/yellowish
5	0.55	Yellowish
Reference 1	3.5	Dark/ brownish
Reference 2	10.5	Dark

10 * Index is calculated as $(\text{Abs}(24\text{hrs}) - \text{Abs}(0\text{hrs})) / \text{Abs}(0\text{hrs})$

** Subjective visual assessment

EXAMPLE 8

Preparation of a PVP-gel comprising silver nitrate.

- To 91 ml of purified water at an ambient temperature was added 500 microliter
 15 1.5M AgNO₃ and 3.75 ml of 2M TRIS (trihydroxymethyl aminomethane). The pH was adjusted to 7.5 by adding diluted nitric acid. Then 5 g of polyvinyl pyrrolidone (K-90 from ISP) was added under vigorous shaking. The mixture was then allowed to rest until all entrapped air has disappeared.

The resulting gel was sterilised with 3 x 11 kGy beta radiation, rendering a slightly
 20 yellowish and light stable gel.

CLAIMS

1. A stabilised composition having antibacterial, antiviral and/or antifungal activity characterised in that it comprises a silver compound and that the compound is in the form of a complex with a primary, secondary or tertiary amine which complex
5 is associated to one or more hydrophilic polymers.
2. A composition as claimed in claim 1, characterised in that the amine is a primary, secondary or tertiary lower alkyl amine or amino alcohol.
3. A composition as claimed in claim 1 or 2, characterized in that the composition has a neutral pH.
- 10 4. A composition as claimed in any of claims 1 - 3, characterised in that the hydrophilic polymers or part of them form a cross-linked network.
5. A composition as claimed in any of claims 1 - 4, characterised in that the hydrophilic polymer is selected from synthetic hydrophilic polymers and deriva-
---tives of animal or vegetable hydrophilic polymers.
- 15 6. A composition as claimed in claim 5, characterised in that the hydrophilic polymers form a gel or xerogel.
7. A composition as claimed in any of claims 1 - 6, characterised in that the hydrophilic polymer network comprises polyvinylpyrrolidone, polyvinyl ether, polyvinyl alcohol, polyurethanes, polyacrylates or polyacrylamides, collagen,
20 gelatine, glucosaminoglucanes, or modified polysaccharides.
8. A composition as claimed in any of claims 1 - 7, characterised in that the silver compound is silver nitrate, silver acetate or silver lactate.

9. A composition as claimed in claim 8, characterised in that the concentration of silver is from 0.1 to 30 % by weight of the dry matter.
10. A medical device comprising an impregnation or coating comprising a silver compound in the form of a complex with a primary, secondary or tertiary amine
5 which complex is associated to one or more hydrophilic polymers.
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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 2/16, A61L 15/46, A61L 33/00

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61L, A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0596615 A1 (MEDTRONIC, INC.), 11 May 1994 (11.05.94) --	1-10
A	File WPI, Derwent accession no. 1988-178826, NIPPON ZEON KK: "Wound-covering material preventing exudation, etc. - comprises fine-pore film layer or poly:aminoacid and core of fibre or metallic net, contg. antibacterial and biocompatible materials"; & JP,A,63115566, 19880520, DW198826 --	1-10

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

28/09/99

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